Corneal Collagen Cross-Linking in Pediatric Patients: Ten Year Experience

Cross-Linking Corneano em Idade Pediátrica: Dez Anos de Experiência

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ABSTRACT

INTRODUCTION: Keratoconus (KC) is a corneal ectatic disorder characterized by progressive corneal thinning and steepening. Corneal collagen cross-linking (CXL) uses riboflavin and ultraviolet-A radiation to induce cross-links in the stromal collagen, increasing its biomechanical rigidity and halting the progression of KC. Different protocols of CXL have been proposed throughout the years to improve clinical results and patient comfort. However, management of pediatric cases remains particularly challenging because younger patients tend to exhibit a more rapid progression of the disease. In this study we aim to evaluate the efficacy of CXL in a population of pediatric patients aged 18 years or less with progressive KC.

MATERIAL AND METHODS: Multi-center, retrospective, cross-sectional study. Patients with progressive KC, aged ≤ 18, who underwent CXL between 2010 and 2021 were reviewed. Different modalities of CXL were used: Standard CXL, Accelerated CXL, Combined CXL and partial topography-guided PRK (photorefractive keratectomy), and Customized CXL. Evaluation included best spectacle corrected visual acuity (BSCVA), manifest refraction, and Scheimpflug tomography evaluation. Baseline and follow-up values were compared.

RESULTS AND DISCUSSION: The study included 44 eyes of 33 patients, 26 (78.8%) male and 7 (21.2%) female. Mean age at time of CXL was 15.2±3.1 years [range 10-18]. Conventional CXL was performed in 9 eyes, and accelerated CXL in 14 eyes. Seven eyes performed combined CXL and simultaneous topography guided PRK. Fourteen eyes performed customized irradiation CXL. Epithelium was removed before CXL in all patients. Mean follow-up was 21.9±16.6 months [range 4-66]. At the last follow-up, mean BSCVA was improved from 0.43±0.26 to 0.38±0.25 LogMAR (p=0.067). Preoperative mean spherical equivalent increased from -1.97±2.44 to -2.41±3.60 D (p=0.509) and cylinder decreased from 2.85±1.92 to 2.34±1.77 D (p=0.045). The flat keratometric values (K1) remained stable, from 48.04±4.87 to 48.74±5.12 D (p=0.358), as well as the steep keratometric values (K2), from 53.63±6.60 to 53.98±6.09 D (p=0.721), and maximum keratometry values (K max), from 62.45±10.38 to 62.20±10.01 D (p=0.764). Thinnest corneal thickness decreased from 452.03±39.63 to 423.59±43.17 µm (p<0.001). Mean spherical equivalent increased in conventional CXL eyes, and had a greater decrease in those having undergone combined CXL and PRK (p=0.042). Thinnest corneal thickness decreased more significantly in the combined CXL and PRK

eyes (p<0.001). No other differences between different CXL protocols were significant. Success rate at the last follow-up was 90.9%, with 4 eyes (9.1%) showing progression after CXL: 2 following accelerated CXL and 2 following customized irradiation CXL.

CONCLUSION: CXL seems to halt the progression of KC in pediatric patients and result in stabilization of visual acuity and topographic parameters. Our results are in line with the published international series for pediatric KC, showing overall good results but more risk of progression than adult patients. Alternative protocols seem to be equally effective as standard-CXL in pediatric KC.

KEYWORDS: Child; Cross-Linking Reagents; Keratoconus; Photochemotherapy.

RESUMO

INTRODUÇÃO: O queratocone (QC) é uma doença ectásica corneana que se caracteriza por um adelgaçamento e encurvamento corneanos progressivos. O *cross-linking* corneano (CXL) utiliza riboflavina e radiação ultravioleta-A para induzir ligações cruzadas no colagénio estromal, aumentando a sua rigidez biomecânica e impedindo a progressão do QC. Ao longo dos anos, diferentes protocolos de CXL foram propostos para melhorar resultados clínicos e o conforto dos doentes. Contudo, a orientação de casos pediátricos permanece particularmente desafiante, uma vez que doentes mais novos tendem a demonstrar progressão mais rápida da doença. Neste estudo pretendemos avaliar a eficácia do CXL numa população de doentes pediátricos com 18 anos ou menos, com QC em progressão.

MATERIAL E MÉTODOS: Estudo multicêntrico, retrospetivo, *cross-sectional*. Os processos dos doentes com QC em progressão, com idade ≤ 18 anos, que foram submetidos a CXL entre 2010 e 2021 foram revistos. Diferentes modalidades de CXL foram utilizadas: CXL *standard*, CXL acelerado, CXL combinado com PRK (*photorefractive keratectomy*) parcialmente topoguiado, e CXL customizado. A avaliação incluiu melhor acuidade visual corrigida (BSCVA), refração subjetiva e tomografia Scheimpflug. Os valores base e no *follow-up* foram comparados.

RESULTADOS E DISCUSSÃO: O estudo incluiu 44 olhos de 33 doentes, 26 do sexo masculino (78,8%) e 7 (21,2%) do sexo feminino. A idade média à data do CXL foi 15,2±3,1 anos [entre 10-18]. CXL convencional foi feito em 9 olhos, e CXL acelerado em 14 olhos. Sete olhos foram submetidos a CXL combinado com PRK, e 14 olhos a CXL com irradiação customizada. O epitélio foi removido previamente ao CXL em todos os doentes. O *follow-up* médio foi de 21,9±16,6 meses [entre 4-66]. À data do último *follow-up*, a BSCVA média melhorou de 0,43±0,26 para 0,38±0,25 LogMAR (p=0,067). O equivalente esférico médio pré-operatório aumentou de -1,97±2,44 para -2,41±3,60 D (p=0,509) e o cilindro diminuiu de 2,85±1,92 para 2,34±1,77 D (p=0,045). Os valores do meridiano mais plano (K1) mantiveram-se estáveis, de 48,04±4,87 para 48,74±5,12 D (p=0,358), bem como os do meridiano mais curvo (K2), de 53,63±6,60 para 53,98±6,09 D (p=0,721), e os valores do ponto de curvatura máxima (K max.), de 62,45±10,38 para 62,20±10,01 D (p=0,764). A espessura corneana no ponto mais fino diminuiu de 452,03±39,63 para 423,59±43,17 μm (p<0,001). O equivalente esférico médio aumentou nos olhos com CXL convencional, e teve uma maior diminuição naqueles submetidos a CXL e PRK combinados (p=0,042). A espessura de córnea mais fina diminuiu mais significativamente nos olhos com CXL combinado com PRK (p<0,001).

Não houve outras diferenças significativas entre os diferentes protocolos de CXL. A taxa de sucesso no último *follow-up* foi de 90,9%, com 4 olhos (9,1%) a demonstrar progressão após o CXL: 2 após CXL acelerado e 2 após CXL com irradiação customizada.

CONCLUSÃO: O CXL parece parar a progressão do QC em doentes pediátricos e resultar na estabilização da acuidade visual e parâmetros topográficos. Os nossos resultados encontram-se em linha com as series internacionais publicadas para QC pediátrico, mostrando globalmente bons resultados mas com maior risco de progressão do que em doentes adultos. Os protocolos alternativos parecem ser igualmente eficazes ao CXL *standard* no QC pediátrico.

PALAVRAS-CHAVE: Criança; Fotoquimioterapia; Queratocone; Reagentes de Ligações Cruzadas.

INTRODUCTION

Keratoconus is a degenerative, bilateral and frequently asymmetric corneal ectatic disorder that leads to progressive corneal thinning and steepening in a cone-like shape.[1] This results in myopia, irregular astigmatism and central corneal scarring, contributing to vision loss. Management of pediatric KC cases is particularly challenging, since young age is associated with faster progression and more severe forms of KC.[2-4] Pediatric patients were found to have a sevenfold higher risk of requiring corneal transplant in the future.[5] Therefore, early diagnosis and effective treatment are especially important in these cases.

Corneal collagen cross-linking (CXL) is a procedure that uses the interaction of riboflavin, which acts as a photosensitizer, and ultraviolet-A radiation to induce crosslinks in the stromal collagen, due to the formation of reactive oxygen species, and thus, new covalent bonds between collagen molecules.[6] This leads to increased corneal stromal rigidity and resistance, and a long-term stabilizing effect, thereby slowing or halting the progression of keratoconus and corneal ectasia.[7,8]

Different protocols of CXL have been proposed throughout the years to improve clinical results and patient comfort. CXL has been successfully performed for years in the treatment of KC, with conventional CXL having demonstrated long-term safety and efficacy in adults with progressive KC after 10 years of follow-up.[9] Various studies have also shown satisfactory outcomes of standard and accelerated CXL treatment in pediatric patients, stabilizing the disease and reducing the need for future corneal graft.[10]

The aim of this study was to evaluate the efficacy of CXL in a population of pediatric patients aged 18 years or less with progressive KC, as well as compare different CXL treatment protocols.

MATERIAL AND METHODS

The files of patients aged 18 or under, who were diagnosed with progressive keratoconus and had been treated with CXL, between 2010 and 2021 in two centers in Coimbra, Portugal, were retrospectively reviewed. KC was considered progressive if the 2 or more of the following criteria were met: increase in Kmax or Kmean of more than 1 D; decrease in central corneal thickness exceeding 5% or 20 µm; increase in manifest myopia, astigmatism, or spherical equivalent superior to 1 D; increase in posterior elevation exceeding 15 µm; decrease of more than 1 Snellen line of best corrected visual acuity.

CLINICAL ASSESSMENT

The study included 44 eyes of 33 patients. Best spectacle corrected visual acuity (BSCVA) was determined using a Snellen chart and then converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Ophthalmological evaluation also included manifest refraction and slit lamp examination. Scheimpflug tomography of the cornea was done. Keratometry values (flat-K1, steep-K2, maximum-Kmax) and corneal thickness at the thinnest point (TCT) were recorded. Baseline and follow-up values were compared.

SURGICAL PROCEDURE

All CXL procedures were performed under sterile conditions and topical anesthesia, using oxybuprocaine hydrochloride 0.4% drops. After the procedures, a bandage contact lens was placed until re-epithelization was achieved. Patients were prescribed ofloxacin and fluorometholone drops, as well as artificial tears.

Patients performed either conventional CXL (Group 1), accelerated CXL (Group 2), combined CXL and partial topography-guided PRK (Group 3) or customized topography-guided CXL (Group 4).

Surgical methods for each treatment protocol are laid out below.

Group 1 (conventional CXL):

The central 9 mm corneal epithelium (depth 50 µm) was removed using either PTK (phototherapeutic keratectomy) or manual epithelial debridement. After a 30-minute riboflavin soak, with riboflavin 0.1% solution applied every 5 minutes, ultraviolet-A (UVA) irradiation of 3 mW/cm2 irradiance was applied for 30 minutes to achieve a total dose of 5.4 J/cm^2.

Group 2 (accelerated CXL):

The central 7 mm corneal epithelium (depth 50 µm) was removed using either PTK (phototherapeutic keratectomy) or manual epithelial debridement. After a 10-minute riboflavin presoak, with riboflavin administered every 2 minutes, UVA was applied using 10 mW/cm^2 for 10 minutes (6 J/cm^2 total dose).

Group 3 (combined CXL and partial topography-guided PRK):

The central 7 mm corneal epithelium (depth 50 µm) was removed using PTK. Partial topography-guided PRK was done after PTK, followed by application of mitomycin C at 0.02% for 20 seconds, and the accelerated CXL protocol.

Group 4 (customized topography-guided CXL):

The central 7 mm corneal epithelium (depth 50 µm) was removed using PTK. Customized CXL using a concentric irradiation pattern of 10 mW/cm2 of energy fluence and total energy dose ranging from 5.4 J/cm^2 up to 10 J/cm^2, with the highest levels centered on the thinnest point of the cornea.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software. Shapiro-Wilk test and histogram plots were used to determine data normality. Preoperative and postoperative continuous variables were compared using Paired Samples T-test or Wilcoxon Signed-Ranks test, according to the distribution of the values. One Way ANOVA test was performed to compare the differences between different CXL protocols. A p value < 0.05 was considered statistically significant.

RESULTS

POPULATION

Forty-four eyes of 33 patients were included. There were 26 (78.8%) male patients and 7 (21.2%) female. Mean age at time of CXL was 15.2±3.1 years, ranging from 10 to 18 years old. Patient demographics are shown in Table 1. The mean follow-up period was 21.9±16.6 months, ranging from 4 to 66 months.

At baseline, mean BSCVA was 0.43±0.26 LogMAR, spherical equivalent (SE) was -1.97±2.44 D and manifest cylinder was 2.85±1.92 D. The mean preoperative flat keratometric value (K1) was 48.04±4.87 D, steep keratometric value (K2) of 53.63±6.60 D, and maximum keratometry value (Kmax) of 62.45±10.38 D. Mean baseline thinnest corneal thickness (TCT) was 452.03±39.63 µm.

Conventional CXL was performed in 9 eyes, and accelerated CXL in 14 eyes. Seven eyes were submitted to combined CXL and simultaneous topography guided PRK. Customized irradiation CXL was done in 14 eyes. Epithelium was removed before CXL in all patients.

Table 1. Patient demographics and characteristics.

Variables	Value
Age (years)	15.2±3.1
Male:female	26:7
Right:left	21:23

REFRACTION AND VISUAL ACUITY

At the last postoperative follow-up, overall mean BSCVA improved slightly from 0.43±0.26 to 0.38±0.25 LogMAR, however the difference was not statistically significant (p=0.067). After CXL, overall mean spherical equivalent became more myopic, with a non-significant increase in absolute value, from -1.97±2.44 to -2.41±3.60 D (p=0.509). Overall mean manifest cylinder decreased significantly from 2.85±1.92 to 2.34±1.77 D (p=0.045).

Visual outcomes and refractive changes in the different treatment groups are displayed in Table 2.

TOMOGRAPHY

Overall keratometric changes between baseline and last follow-up were reviewed, and none of the keratometric values showed statistically significant differences. The flat keratometric values (K1) remained stable from 48.04±4.87 to 48.74±5.12 D (p=0.358), as well as the steep keratometric values (K2), from 53.63±6.60 to 53.98±6.09 D (p=0.721), and maximum keratometry values (K max), from 62.45±10.38 to 62.20±10.01 D (p=0.764).

A statistically significant reduction in overall thinnest corneal thickness was found at the time of last follow-up compared to preoperative values, decreasing from 452.03±39.63 to 423.59±43.17 µm (p<0.001).

Tomographic value changes in the different treatment groups are shown in Table 3.

CXL MODALITIES

As seen in Table 4, mean spherical equivalent had a significant hyperopic shift in conventional CXL eyes, and suffered significantly greater myopization in those having undergone combined CXL and PRK (p=0.042). Thinnest corneal thickness was more significantly reduced in the combined CXL and PRK eyes, and was less decreased in customized CXL patients (p<0.001). No other differences between differ-

Table 2. Visual outcomes and refractive changes in different treatment groups.

Variables	Conventional CXL			Accelerated CXL			Combined CXL+PRK			Topography guided CXL		
	PreO p	PostOp	p	PreOp	PostOp	p	PreOp	PostOp	p	PreOp	PostOp	p
BSCVA (LogMAR)	0.40±0.24	0.55±0.27	0.256	0.47±0.35	0.42±0.28	0.507	0.47±0.26	0.34±0.11	0.163	0.39±0.19	0.24±0.19	0.020
SE (D)	-1.53±0.76	-0.72±1.54	0.136	-3.18±3.32	-3.21±3.28	0.842	-3.20±1.84	-6.07±5.26	0.208	-0.51±1.58	-0.87±2.33	0.426
Cyl (D)	2.67±1.26	3.00±1.09	0.598	2.98±2.14	1.95±1.64	0.091	3.82±3.08	2.79±3.03	0.028	2.38±1.20	2.09±1.43	0.332

CXL – corneal collagen cross-linking; PreOp – preoperative values; PostOp – postoperative values; BSCVA – best spectacle corrected visual acuity; SE – spherical equivalent; Cyl – manifest cylinder.

Table 3. Tomography value differences in different treatment groups.

Variables	Conventional CXL			Accelerated CXL			Combined CXL+PRK			Topography guided CXL		
	PreO p	PostOp	p	PreOp	PostOp	p	PreOp	PostOp	p	PreOp	PostOp	p
K1 (D)	46.06±3.64	47.05±4.46	0.664	50.25±4.65	51.46±4.91	0.160	49.73±4.00	49.93±3.14	0.852	46.13±5.33	45.94±5.14	0.913
K2 (D)	51.43±6.20	52.97±7.14	0.664	56.63±5.13	57.26±6.37	0.587	56.99±7.08	54.17±3.69	0.149	50.11±6.24	50.82±4.98	0.791
TCT (µm)	445.3±29.2	408.0±24.0	0.012	434.2±37.1	409.0±39.7	<0.001	463.9±39.5	404.6±32.4	0.002	472.4±39.9	459.5±41.2	0.014

CXL – corneal collagen cross-linking; PreOp – preoperative values; PostOp – postoperative values; K1 – flat keratometric values; K2 – steep keratometric values; TCT – thinnest corneal thickness.

Table 4. Variable changes after CXL in different treatment groups.

Variation*	Conventional CXL	Accelerated CXL	Combined CXL+PRK	Topography guided CXL	*p* value
SE (D)	0.81±1.46	-0.08±1.36	-2.88±5.39	-0.36±1.63	0.042
Cyl (D)	0.33±1.82	-0.82±2.37	-1.04±0.95	-0.20±1.14	0.333
K1 (D)	0.28±1.50	1.21±3.03	0.20±2.72	-0.55±0.79	0.292
K2 (D)	-0.32±1.68	0.63±4.23	-2.17±3.69	0.45±1.59	0.273
TCT (μm)	-37.2±23.7	-25.2±18.2	-59.3±30.1	-9.8±11.7	<0.001

*Variable variation, comparing postoperative values with preoperative values. CXL – corneal collagen cross-linking; BSCVA – best spectacle corrected visual acuity; SE – spherical equivalent; Cyl – manifest cylinder; K1 – flat keratometric values; K2 – steep keratometric values; TCT – thinnest corneal thickness.

ent CXL protocols reached statistical significance.

Success rate at the last follow-up was 90.9%, with 4 eyes (9.1%) showing progression after CXL: 2 following accelerated CXL and 2 following customized irradiation CXL.

DISCUSSION

Given the more aggressive course of disease in pediatric KC, various authors have proposed that early diagnosis and treatment of KC are crucial for halting progression, preventing development of complications and thus preserving the best possible visual acuity in pediatric patients.[4,11,12] It has been proposed by several authors that CXL is both safe and effective when used to prevent keratoconus progression in pediatric patients.[8,11,13-15]

In our pediatric population, CXL was apparently effective, with stable results in 90.9% of patients at last follow-up. Keratometric and visual acuity values remained stable after CXL treatment, with no statistically significant differences between pre and postoperative values.

We found a progression rate at the last follow-up of 9.1% (4 eyes), which is slightly better than other pediatric CXL studies. Mazzotta et al reported an overall progression rate of 20% of eyes after conventional CXL in pediatric patients, similarly to Godefrooij et al, who found progression in 22% of eyes after the same CXL protocol.8,11 Padmanabhan et al studied 377 eyes of pediatric KC patients that underwent conventional CXL, and reported that, after 4 years, 24% of eyes showed steepening of the cornea, and 30.9% showed reduction in visual acuity.[13] In our study, two eyes underwent corneal ring implantation after CXL due to poor spectacle corrected visual acuity, not to keratoconus progression, and were, thus, not included in progression percentage.

A meta-analysis and systematic review which included relevant studies on the effects of standard, transepithelial, and/or accelerated CXL protocols in patients aged 18 years or younger concluded that all CXL techniques slowed disease progression in patients with pediatric KC for at least 1 year.[10] A significant hyperopic shift in conventional CXL at 1 year was found, and possibly attributed to a significant flattening of Kmax.[10] Our results are in accordance with this finding, showing a significant hyperopic shift at the last follow-up visit in the standard CXL group, in comparison with other CXL protocols.

Previous studies have reported a significant decrease in TCT after CXL treatment alone.[16,17] However, studies have also shown an increase after approximately 12 months following the procedure, with corneal thickness values returning to baseline values.[13,17,18] In our sample, we found a decrease in mean TCT after CXL, with greater reduction in the group that performed combined CXL and partial topography-guided PRK. This was to be expected since PRK removes corneal tissue, thus leading to a reduction in corneal thickness.

Our analysis of the changes in variable values after different CXL modalities showed that significant differences were a greater hyperopic shift in conventional CXL eyes versus more significant myopization in combined CXL and PRK eyes, and a larger reduction in TCT in combined CXL and PRK eyes versus less marked decrease in customized topography guided CXL. Even if the statistical significance was marginal, there was a marked clinical difference regarding visual acuity improvement, favoring customized treatments with either adjuvant topography guided PRK or applying topography guided irradiation patterns. This clinical difference is particularly important since no discernable loss of efficacy was noted regarding biomechanical stabilization. There were no other significant differences between various protocols.

Accelerated CXL uses greater UVA irradiance intensity with lower total exposure time, compared to the conventional protocol.14 The accelerated method may be preferred over the standard protocol given the shorter procedure duration, which represents a major advantage in pediatric patients, especially those who are younger or less cooperative.[19] Although the superiority of accelerated CXL treatment over the conventional protocol is not entirely clear, studies have found that accelerated CXL treatment seems to be at least as effective and safe as standard CXL in pediatric KC patients.[14,19,20] A prospective study of 39 eyes of pediatric KC patients, with a follow-up of 4 years, found that the long-term results of combined CXL and PRK seem to be safe and effective in pediatric patients.[21] Topography guided CXL is the most recent advance in corneal collagen cross-linking. Its ability to combine disease stabilization and visual improvement, with no need for tissue ablation, could make it a very powerful tool in our armamentarium

of KC treatment. To our knowledge, ours is the first reported cohort of pediatric patients treated with this technique.

The first limitation of our study was its retrospective nature. The large range of different follow-up periods is also a confounding factor when comparing last follow-up variable values. Despite these limitations, we believe this study provides relevant information on the results of different CXL modalities in pediatric KC patients.

In conclusion, CXL seems to halt the progression of KC in pediatric patients and result in stabilization of visual acuity and topographic parameters. Our results are in line with the published international series for pediatric KC, showing overall good results but more risk of progression than adult patients. Alternative protocols seem to be equally as effective as standard-CXL in pediatric KC.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

RF: Colheita de dados, análise estatística, elaboração do manuscrito e aprovação da versão final.

GG: Colheita de dados, aprovação da versão final.

JG, EC, AR, CT, MJQ, JM: Conceptualização, revisão crítica do conteúdo; aprovação da versão final.

RESPONSABILIDADES ÉTICAS

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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